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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,797	02/17/2004	David Munn	275.00100101	1508

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,797	MUNN ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-13 and 30-39* is/are pending in the application.

4a) Of the above claim(s) *5-7,10,12 and 35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,11,13 and 30-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *15 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7, 9-13, and 30-39 are presented for examination

Applicants' amendment filed 9/28/2007 and Information Disclosure Statements filed 3/20/2007 and 9/28/2007 have been received and entered into the application. Accordingly, claims 1, 3-5, 10-12, 30, and 32-37 have been amended, claims 8, 14, 19, and 24-29 have been cancelled, and claims 38-39 have been added. Also, as reflected by the attached, completed copy of USPTO Form 1449 the cited references have been considered.

Applicants' arguments, filed 9/28/2007, have been fully considered and are persuasive in part. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new rejections being applied against the pending claims, this Office Action is **Non-Final**.

Election/Restrictions

Applicants' request for rejoinder of Group III (claims 32 and 34) and Group IV (claims 35 and 37) with elected Group I (pages 9-10 of Response) has been considered and is persuasive. Accordingly, the restriction between Groups I, III, and IV as set forth in the Requirement for Election/Restriction mailed 12/20/2006 is hereby **withdrawn**. The Species Election requirement is still deemed proper and is maintained for the reasons of record. The elected species are 1-methyl-tryptophan as the IDO inhibitor and cyclophosphamide as the additional

chemotherapeutic agent. Claims 5-7, 10, 12, and 35-39 are withdrawn from consideration as being drawn to a non-elected species (*i.e.*, radiation therapy).

Priority

This application claims the benefit of U.S. Provisional Application Serial No. 60/459,489, filed April l, 2003 and U.S. Provisional Application Serial No. 60/538,647, filed January 22, 2004. Applicants' arguments are persuasive that 60/538,647 provides support for inhibitors of indoleamine-2,3-dioxygenase other than D isomers of inhibitors of indoleamine-2,3-dioxygenase (see page 33, line 26 to page 34, line 11; Figure 7; page 8, line 20; page 12, line 30 to page 13, line 6; page 31, lines 22-26). Accordingly, the instant claims are afforded a priority date of April 1, 2003.

Oath/Declaration

Receipt is acknowledged of the replacement Declaration executed by Andrew Mellor, filed 9/28/2007.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, the limitation "previously known to be therapeutically effective

for the treatment of said cancer" renders the claim unclear as to what agents are and are not included by this limitation. Recitation of "previously known" suggests that there is a specific point in time when a particular agent becomes "known". However, it is unclear when this point in time is and whether "previously known" only refers to those chemotherapeutic agents that were known before Applicants' invention or those agents that are discovered later, but are "previously known" to a reader of the claims at some future date.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 9, 11, 13, and 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/66764 (previously cited) and Tsung *et al.* (The Journal of

Immunology, 1998, vol. 160, pages 1369-1377) (newly cited) in view of Pinedo *et al.* (The Oncologist, 2000, vol. 5, pages 497-500) (newly cited).

The invention relates to the treatment of cancer in a subject (*e.g.*, claim 1), augmenting tumor cell rejection in a subject (*e.g.*, claim 32), or reducing tumor size or tumor growth in a subject (*e.g.*, claim 34) comprising administering 1-methyl-tryptophan and cyclophosphamide. The specification and claims state that such a combination will be synergistic (*i.e.*, the effect of the combination is greater than that of either agent alone).

WO '764 teaches methods for increasing T cell proliferation comprising administering a tryptophan-enhancing agent (Abstract). Suitable tryptophan-enhancing agents include inhibitors of indoleamine-2,3-dioxygenase (IDO) (page 1, lines 18-21). Preferred IDO inhibitors include 1-methyl-tryptophan, β-(3-benzofuranyl)-alanine and β-[3-benzo(*b*)thienyl]-alanine (page 2, lines 12-15 and page 6, line 30 to page , line 10) as recited in the instant claims. The reference further teaches methods of treating cancer comprising administering an inhibitor of indoleamine-2,3-dioxygenase so as to elicit a T-cell response (*i.e.*, increased T-cell-mediated cytolysis of cancer cells (page 3, lines 30-33; page 18, lines 4-19 and lines 25-29). Tumor cells are shown to express IDO constitutively (see Examples). As such, WO '764 contemplates that inhibition of IDO can be used to increase a subject's immune response, leading to lysis of antigen presenting cells, such as cancer cells which present one or more cancer associated antigens (page 15, lines 12-14). The IDO inhibitors can be administered as a component of an immune response modulation composition, *i.e.*, in combination with another therapeutic agent (page 16, lines 22-23). Additional therapeutic agents can include T cells, antigens (*e.g.*, peptides, proteins), nucleic acids encoding antigens (*id.* at lines 25-27). Cytokines, including GM-CSF (as recited in instant

claims 30-31) and IL-12 are taught to be useful in the immune response modulation compositions (page 17, lines 11-18). Cancers constitutively expressing IDO are taught to reduce the local concentration of tryptophan and disable T-cell-mediated immune response to the cancer (page 17, lines 26-29). As such, WO '764 teaches that administering a tryptophan enhancing agent (such as an IDO inhibitor) will result in an increase in T-cell-mediated cytolysis of the cancer cell (*id.* at lines 31-33). Leukemia, mastocytoma, melanoma, and renal cancer cells were found to constitutively express IDO (page 21, lines 25-27). Table 1 also demonstrates that other tumor cell lines, including colon, pancreatic, breast, lung, sarcoma, and ovarian as recited in claims 13 and 39, also constitutively express IDO. WO '764 does not explicitly teach combining inhibitors of IDO with cytotoxic antineoplastic chemotherapy agents (*e.g.*, cyclophosphamide) as instantly claimed.

Tsung *et al.* teach that a combination of cytokine IL-12 and the cytotoxic agent cyclophosphamide completely eradicates murine MCA207 sarcomas that are refractory to treatment with either IL-12 or cyclophosphamide alone, thus motivating combining these agents for treating sarcomas (Abstract; Table 1).

Pinedo *et al.* discuss biological concepts of prolonged neoadjuvant treatment plus GM-CSF in locally advanced tumors. In this regard, it is disclosed that in patients with locally advanced breast cancer, a dysfunction of dendritic cells leads to a general immunosuppressive state with depressed T-cell reactivity (page 498, right column). Chemotherapy is disclosed to reduce the production of tumor-derived immunosuppressive factors, enabling the initiation of tumor-specific cytotoxic T-cell responses (page 498, right column) as well as to induce tumor cell necrosis and apoptosis, both of which cause release of antigen (*id.*).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instantly claimed methods would have been *prima facie* obvious to one of ordinary skill at the time the invention was made. In support of the obviousness of the instantly claimed methods of treating cancer, the Examiner makes the following findings of fact:

a) The prior art motivates the use of IDO inhibitors, including 1–methyl-tryptophan, for the treatment of cancers, especially those that constitutively express IDO. Administration of an IDO inhibitor to a cancer patient is suggested to increase a subject's immune response, leading to lysis of antigen presenting cells, such as cancer cells which present one or more cancer associated antigens (WO '764, page 15, lines 12-14);

b) It was known in the art that cyclophosphamide combined with IL-12 is more effective than either agent alone due to immunopotentiation of delayed-type hypersensitivity in sarcomas resulting from cyclophosphamide (Tsung *et al.*); and

c) It was known in the art that chemotherapy leads to a reduction in the production of tumor-derived immunosuppressive factors, enabling the initiation of tumor-specific cytotoxic T-cell responses as well as an induction of tumor cell necrosis and apoptosis, both of which cause release of antigen (Pinedo *et al.*).

In view of the above findings, the skilled artisan would have been imbued with at least a reasonable expectation that administration of 1-methyl-tryptophan and cyclophosphamide, optionally combined with a cytokine, would result in an effective treatment of cancer. As taught in WO '764, 1-methyl-tryptophan would be expected to increase a subject's immune response (*via* inhibition of IDO), leading to lysis of antigen presenting cells, such as cancer cells which present one or more cancer associated antigens. Addition of a cytotoxic chemotherapeutic agent such as cyclophosphamide would be expected to reduce the production of tumor-derived immunosuppressive factors, enabling the initiation of tumor-specific cytotoxic T-cell responses as well as to induce tumor cell necrosis and apoptosis, both of which would cause release of antigens from tumor cells. Finally, the cytotoxic T-cell response initiated by cyclophosphamide would be further enhanced by the increased T-cell proliferation induced by inhibition of IDO by 1-methyl-tryptophan as taught in WO '764.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 10/780,150

Claims 1-4, 9, 11, 13, 30-31, and 33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-10 and 17-26 of copending Application No. 10/780,150. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims encompass the subject matter claimed in the '150 patent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

December 6, 2007

/Ardin H. Marschel/ 12/9/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER